CJASN ePress. Published on November 6, 2018 as doi: 10.2215/CJN.07850618

Perspective

Intravenous Fluids
Finding the Right Balance

Paul M. Palevsky

Clin J Am Soc Nephrol 13: ●●●–●●●, 2018. doi: https://doi.org/10.2215/CJN.07850618

Administration of intravenous fluids is common in the management of acute illness; however, despite their ubiquitous use, rigorous evidence regarding their optimal composition and administered volume is limited. Two studies (the Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department [SALT-ED] Study and the Isotonic Solutions and Major Renal Events Trial [SMART]) published earlier this year concluded that use of "balanced" crystalloid solutions rather than isotonic (0.9%) saline was associated with reductions in mortality and AKI (1,2), leading to suggestions that the routine use of isotonic saline should be abandoned (3).

Concerns regarding isotonic saline are not new. In a series of experiments in dogs published more than three decades ago, Wilcox (4) showed that hyperchloremia induced by infusions of sodium or ammonium chloride resulted in renal vasoconstriction and decreased renal blood flow and GFR. These effects were not seen with infusions of similar volumes of sodium bicarbonate, sodium or ammonium acetate, or dextrose. The vasoconstriction associated with sodium chloride infusion was augmented if the dogs were initially volume depleted. Similarly, renal blood flow velocity and cortical perfusion, assessed using magnetic resonance imaging, were reduced in healthy adults after infusion of isotonic saline compared with equal volumes of a balanced electrolyte solution (5). However, these changes in renal perfusion were not associated with differences in the concentration of urinary neutrophil gelatinase–associated lipocalin. Saline infusion has also been associated with exacerbation of AKI in a rat model of sepsis (6).

Prior clinical trials have, however, yielded conflicting results (7–9). In a prospective, single-center, open label trial, outcomes among 760 patients treated for 6 months when access to isotonic saline and other "high-chloride" fluids was unrestricted were compared with outcomes among 773 patients treated during a subsequent 6-month period when balanced electrolyte solutions were used (7). Compared with the initial period, the incidence of AKI and the use of kidney replacement therapy (KRT) decreased after the switch to balanced electrolyte solutions. Although this trend was still present after extending the observation periods by an additional 6 months and including an additional 1441 patients, variability in the incidence of AKI suggested that the results may have been influenced by unidentified confounding (8). Subsequently, the use of buffered crystalloid did not reduce the risk of AKI or the need for KRT in the 0.9% Saline vs Plasma-Lyte 148 (PL-148) for ICU fluid Therapy (SPLIT) Trial, a cluster-randomized study that enrolled 2278 patients in four intensive care units (ICUs) in New Zealand (9). It has been suggested that the lack of benefit reflected a median administered fluid volume of only 2000 ml.

Both the SALT-ED Study and the SMART were pragmatic, unblinded, cluster-randomized trials conducted at a single academic medical center (1,2). Both compared the use of isotonic saline with that of balanced crystalloid solutions (lactated Ringer's solution or Plasma-Lyte). In both studies, allocation of fluid alternated monthly. Given the pragmatic design of the trials, the need for informed consent was waived, and the key outcomes—major adverse kidney events within 30 days (MAKE30; a composite of in-hospital mortality, receipt of new KRT, or persistent kidney dysfunction defined by a final inpatient serum creatinine ≥200% of baseline) and hospital-free days—were ascertained from the electronic medical record. The SMART enrolled 15,802 patients admitted to five medical and surgical ICUs (1). The MAKE30 end point occurred in 14.3% of patients allocated to balanced fluids compared with 15.4% of those allocated to saline (odds ratio, 0.90; 95% confidence interval, 0.82 to 0.99; $P=0.04$), with the outcome driven primarily by mortality (10.3% versus 11.1%; $P=0.06$) and new KRT (2.5% versus 2.9%; $P=0.08$). The SALT-ED Study, which ran concurrently, enrolled 13,347 noncritically ill patients who received at least 500 ml of intravenous fluids in the emergency department and were subsequently hospitalized outside of an ICU (2). As in the SMART, fluid assignment alternated by month. No difference was observed in the primary outcome of hospital-free days, but balanced fluids were again associated with a lower incidence of the MAKE30 end point (4.7% versus 5.6%; odds ratio, 0.82; 95% confidence interval, 0.70 to 0.95; $P=0.01$), although driven primarily by a lower rate of kidney dysfunction (3.8% versus 4.5%).

Important strengths of these two studies are their size, with a total enrollment of >29,000 patients, and the use of a pragmatic design, which favors generalizability to routine clinical practice. However, the pragmatic design, which necessitated cluster randomization by

Renal Section, Medical Service, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; and Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Correspondence:
Dr. Paul M. Palevsky, Renal Section, Veterans Affairs Pittsburgh Healthcare System, Room 7E123 (111F-U), University Drive, Pittsburgh, PA 15240. Email: palevsky@pitt.edu

month and treatment unit, and the use of open label fluids also increased the risk of bias. Several other key limitations must also be recognized. The major adverse kidney events composite is not without its limitations. Optimally, the components of a composite outcome are of similar clinical importance. Although the clinical significance of the components of the major adverse kidney events outcome is clearly disparate, there is good rationale for combining them, because they are competing events. The ascertainment of persistent elevation in serum creatinine on the basis of the last in-hospital value within 30 days may have overestimated this component of the end point. Patients may have been discharged before full recovery of kidney function; thus, it is possible that no difference would have been found if uniformly reassessed at 30 days, particularly given the relatively short median duration of hospitalization in the SALT-ED Study. Because the studies were not powered on the basis of the individual components of MAKE30, it is not unexpected that these components did not reach statistical significance in either trial. It is reassuring, that, in both trials, the trend for all of the components of the composite was in the same direction; however, in the SALT-ED Study, among patients with milder severity of illness, differences in persistent kidney dysfunction predominated, whereas in the patients with higher acuity of illness enrolled in the SMART, the differences in mortality and KRT predominated.

Isotonic saline is not a direct nephrotoxin, along the lines of aminoglycosides or cisplatinum. Rather, given its effects on renal perfusion, its supraphysiologic chloride concentration potentiates other risks of kidney injury, such as hypotension and sepsis. Consistent with this paradigm, the potential benefit of balanced fluids varied significantly across patient subgroups. Although there was no interaction between the volume of fluid administered and outcomes among the noncritically ill patients in the SALT-ED Study, there was a greater treatment effect seen with higher administered volumes among the critically ill patients in the SMART. In noncritically ill patients, the treatment effect was greater in patients who had baseline hyperchloremia or a serum creatinine $\geq$1.5 mg/dl on presentation. In the critically ill patients in the SMART, virtually the entire benefit associated with balanced fluids for both the composite outcome and mortality was restricted to patients with sepsis and patients with higher predicted in-hospital mortality. Although the overall number needed to treat to prevent the composite outcome was 91, among patients with sepsis, it was 20, whereas in patients without sepsis, it was 333.

It should be acknowledged that initial evidence supporting the use of 0.9% saline was limited primarily to documentation of its isotonicity with plasma (10). Although there is nearly a century of clinical experience supporting the general safety and efficacy of isotonic saline, the results of these recent studies should sensitize us to its nonphysiologic composition. However, the limitations of existing balanced crystalloids must also be recognized. For example, both lactated Ringer's ($[Na^+]$ = 130 mmol/L) and Plasma-Lyte ($[Na^+]$ =140 mmol/L) have lower sodium concentrations than plasma water ($[Na^+]$ =145–155 mmol/L), and their use was associated with higher rates of hyponatremia. Both are buffered using organic anions, whose metabolism may be impaired in patients with lactic acidosis, sepsis, or liver failure, and the buffer content of Plasma-Lyte is supraphysiologic and can contribute to metabolic alkalosis.

On the basis of these data, should we broadly abandon the use of isotonic saline, such as has been recommended by some (3)? I would argue that the answer is no. In the majority of patients who have normal kidney function, are not hyperchloremic, do not have sepsis, and require only modest volumes of intravenous fluids, the use of isotonic saline remains reasonable. However, the selection of intravenous fluids, such as is true for other medications, should be individualized. In higher-risk patients, such as those with sepsis, the use of saline should be replaced by balanced fluids. In patients with metabolic acidosis, fluids with an even higher bicarbonate concentration may be indicated. It should be recognized, however, that there are no commercially available fluids that are truly physiologic and that the development of more optimal fluids would be desirable. Although in the past, lack of stability of bicarbonate-buffered solutions was a barrier, such fluids can now be manufactured with a suitable shelf-life. Thus, one can envision a future where the standard intravenous fluid has an electrolyte composition more closely resembling extracellular fluid—for example, with concentrations of sodium of 150 mmol/L, chloride of 120 mmol/L, and bicarbonate of 30 mmol/L. Regardless of the fluid used, we must also learn to be more judicious in our use of intravenous fluids to prevent iatrogenic volume overload.

Acknowledgments

The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or the *Clinical Journal of the American Society of Nephrology* (CJASN). Responsibility for the information and views expressed therein lies entirely with the author(s).

Disclosures

None.

References

1. Semler MW, Self WH, Rice TW: Balanced crystalloids versus saline in critically ill adults. *N Engl J Med* 378: 1951, 2018
2. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW; SALT-ED Investigators: Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med* 378: 819–828, 2018
3. Kellum JA: Abnormal saline and the history of intravenous fluids. *Nat Rev Nephrol* 14: 358–360, 2018
4. Wilcox CS: Regulation of renal blood flow by plasma chloride. *J Clin Invest* 71: 726–735, 1983
5. Chowdhury AH, Cox EF, Francis ST, Lobo DN: A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 256: 18–24, 2012
6. Zhou F, Peng ZY, Bishop JV, Cove ME, Singbartl K, Kellum JA: Effects of fluid resuscitation with 0.9% saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis*. *Crit Care Med* 42: e270–e278, 2014
7. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 308: 1566–1572, 2012
8. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M: Chloride-liberal vs. chloride-restrictive intravenous fluid

administration and acute kidney injury: An extended analysis. *Intensive Care Med* 41: 257–264, 2015
9. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R; SPLIT Investigators; ANZICS CTG: Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: The SPLIT randomized clinical trial. *JAMA* 314: 1701–1710, 2015
10. Matas R: The continued intravenous "Drip": With remarks on the value of continued gastric drainage and irrigation by nasal intubation with a gastroduodenal tube (Jutte) in surgical practice. *Ann Surg* 79: 643–661, 1924

Published online ahead of print. Publication date available at www.cjasn.org.